SURVIVAL AND RISK FACTORS FOR DEATH AMONG HIV-INFECTED ADULTS WITH END-STAGE RENAL DISEASE IN THE UNITED STATES AND CANADA

by

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ABSTRACT

Background: With the advent of highly active antiretroviral therapy, the life expectancy of people living with HIV (PLWH) has approached that of the general population. Nevertheless, aging PLWH are at an increased risk of certain conditions associated with aging, including end-stage renal disease (ESRD). Research characterizing the survival experience of PLWH diagnosed with ESRD is still evolving.

Methods: Data from the North American AIDS Cohort Collaboration for Research and Design (NA-ACCORD) were used to validate incident cases of ESRD among HIV-infected adults occurring from January 1995 to December 2010. Pooled logistic regression was used to identify risk factors for death post-ESRD diagnosis. Kaplan-Meier curves were generated to characterize survival. Standardized mortality ratios (SMRs) by age, sex, and race were calculated to compare mortality between the NA-ACCORD population and the general population using data from the United States Renal Data System (http://www.usrds.org/reference.aspx).

Results: A total of 540 HIV-infected individuals on dialysis, aged 18 to 89, contributed 23,491 person-months, or 1958 person-years, to this analysis. The median age at ESRD diagnosis was 44 years in HIV-infected individuals compared to 60 to 65 years in the general population. The median survival after diagnosis in the NA-ACCORD population was approximately five years. Older age (≥60 years), elevated total cholesterol, history of clinical AIDS diagnosis, CD4+ cell count less than 200 cells/μl, detectable viral load (≥200 copies/mL), no ART use, and tenofovir exposure prior to diagnosis were

associated with an increased hazard of death after ESRD diagnosis. An age-adjusted SMR of 1.09 (95% CI: 0.89, 1.29) suggests that the NA-ACCORD population had approximately the same number of deaths as would be expected if the probability of death in HIV-infected adults with ESRD was the same as in the general population with ESRD.

Conclusions: HIV-related risk factors were more strongly associated with the hazard of death among HIV-infected adults with ESRD compared to traditional age-related risk factors. The median life expectancy post-ESRD diagnosis was similar between HIV-infected and uninfected adults on dialysis, even though HIV-infected adults were diagnosed with ESRD 15 to 20 years younger compared with the general population. After adjusting for age, the mortality experience was similar between both groups.

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BACKGROUND

Since the HIV epidemic began in the early 1980s, survival among infected individuals has steadily improved. With the discovery of highly active antiretroviral therapy (HAART) in the mid-1990s, the average life expectancy for HIV-infected individuals has improved significantly, with estimates approaching that of the general population (The Antiretroviral, 2008; Nakagawa et al., 2012; Samji et al, 2013). Since the early-HAART era, the number of people living with HIV (PLWH) who are 50 years or older has approximately doubled, with over 30% of prevalent HIV cases occurring in this age group in the United States, based on the most recent available data (Mahy et al., 2014; UNAIDS, 2014). The CDC estimates that by 2015, 50% of individuals with HIV in the U.S. will be over 50 years old (National Institute on Aging).

Despite improvements in survival and treatment, however, PLWH are at an elevated risk for non-AIDS related comorbid conditions. For instance, the risk of myocardial infarction, renal failure, liver diseases, hypertension, and hepatitis C is significantly higher in this population than in the general aging population (Hasse et al., 2011; Guaraldi et al., 2011). There are multiple potential explanations for this elevated risk, including the overlapping risk factors for certain comorbidies and HIV, the chronic inflammatory effect of the virus itself, and the toxicities associated with antiretroviral therapy (Deeks, 2009; Deeks, 2011).

End-Stage Renal Disease in the General Population and HIV+ Adults

Renal complications in PLWH are prominent among these comorbid conditions, and they have persisted in the era of antiretroviral therapy. End-stage renal disease

(ESRD) is the last stage of chronic kidney disease and describes the most severe and permanent form of these complications. ESRD is defined as the point in which a patient's kidneys fail to function without the assistance of renal replacement therapy, specifically hemo- or peritoneal dialysis or a kidney transplant. In the United States, individuals automatically qualify for Medicare at diagnosis of ESRD, regardless of age. Medicare and Medicaid cover the cost of dialysis ("Coverage," 2014). The United States Renal Data System (USRDS) collaborates with the Centers for Medicare and Medicaid, among other organizations, to establish full capture of ESRD patients in the U.S. (United States Renal, 2014). In order to characterize trends in survival among HIV+ ESRD patients, the experience among the general U.S. population, as described by USRDS, will serve as the reference group.

USRDS data suggest that the incidence of ESRD among the general population has been plateauing in recent years. In 2012, the number of new cases was approximately 115,000, and the number of prevalent cases was under 650,000 (United States Renal, 2014). There is a notable racial discrepancy among the distribution of ESRD cases, however, with the black population at an over three-fold increased risk of developing this disease compared to the white population (United States Renal, 2014). Overall, the mean age of ESRD patients is estimated to be approximately 60 to 65, with the majority of the disease burden falling on patients over this age (United States Renal, 2014).

ESRD trends among patients with HIV, however, are less well characterized. As previously mentioned, renal complications and ESRD remain prominent among PLWH – particularly aging PLWH. With the advent of HAART and accompanying improvements in HIV management, the incidence of certain ESRD-causing conditions, such as HIV-

Associated Nephropathy (HIVAN), has decreased significantly (Abraham et al., 2014; Ross & Klotman, 2004). Nevertheless, the risk of ESRD remains elevated among PLWH, with estimates suggesting the risk could be up to 20 times higher (Jotwani et al., 2012; Bickel et al., 2013; Abraham et al., 2014). Some of the traditional risk factors for ESRD include high blood pressure, smoking, hepatitis C, and drug use, which are more common among HIV+ individuals (Seaberg et al., 2005; Perneger et al., 2001). However, after accounting for differences in risk factors for ESRD in HIV+ adults and the general population, HIV+ adults still have an increased risk of ESRD compared to similar, uninfected adults (Abraham et al., 2014). In addition, there is evidence to suggest that antiretroviral treatments, specifically tenofovir, increase the risk of renal complications, including ESRD, due to their nephrotoxic effects (Izzedine et al., 2009).

Previous studies have examined the risk factors for developing ESRD among PLWH. As in the general population, black individuals with HIV are at a significantly higher risk of progressing to ESRD (Lucas et al., 2008, Abraham et al., 2014). Comorbid conditions such as hypertension, diabetes, and cardiovascular disease have been identified as risk factors, as have HIV-associated risk factors such as low CD4+ cell count, high HIV viral load, and hepatitis C co-infection (Jotwani et al., 2012).

Mortality After ESRD in the General Population and Among HIV+ Adults

In the general population, survival post-ESRD diagnosis depends on myriad factors, including age, race, and sex. Overall, however, the most recent USRDS data estimate that the 5-year survival is approximately 45% among patients on dialysis, and this trend has been steadily increasing from year to year (United States Renal, 2014).

Research on survival post-ESRD diagnosis in HIV-infected adults has yielded varying estimates of 5-year survival. Many studies do not report 5-year survival, or truncate Kaplan-Meier curves before this time period because so few patients survive beyond this point (Ahuja et al., 2002; Atta et al., 2007). Studies that do report 5-year survival have estimates that range from 9% to 35% (Rodriguez et al., 2003; Soleymanian et al., 2006). However, these studies have follow-up that ended nearly 10 years ago; it is possible that survival has improved since that time.

Objectives

The objectives of the present study were two-fold. First, we aimed to better characterize survival among HIV-infected adults with ESRD. The data, which included verified ESRD cases among PLWH, are representative of individuals linked to care in North America (Althoff et al., 2012). Traditional and HIV-specific risk factors were included as potential risk factors for death among this population. Second, we aimed to compare mortality in HIV+ adults with ESRD to mortality in the general population with ESRD. USRDS data served as the reference group. Research on this topic has been consistently evolving in recent years, perhaps reflecting improvements in HIV management over time. These objectives were meant to further elucidate and expand this area of research.

METHODS

Study Population

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a consortium of single- and multi-site HIV cohorts in the United States and Canada. It was created in 2006 as one of seven members of the International Epidemiological Databases to Evaluate AIDS (IeDEA) network established by the National Institute of Allergy and Infectious Diseases. NA-ACCORD contributing cohorts provide data on both HIV-infected and HIV-uninfected individuals to facilitate research and characterize HIV care across North America. The consortium includes over 25 cohorts and 200 clinical sites, including academic research centers, hospitals, and private practices in the United States and Canada ("North American," 2015; Kitahata et al., 2015). Clinical, demographic, and behavioral data are collected at varying intervals – depending on cohort protocol – and merged at the NA-ACCORD Data Management Core at the University of Washington in Seattle (Gange et al., 2007).

ESRD Validation

12 participating NA-ACCORD cohorts provided clinical data, including patient medical histories, medications, and laboratory measurements, which were utilized to verify cases of end-stage renal disease (ESRD) among HIV+ adults.

The ESRD screening and verification process has been published previously (Kitahata et al., 2015). Briefly, researchers first used a screening algorithm to identify potential HIV+ individuals with ESRD in any of these 12 cohorts. Patients with a positive ESRD diagnosis code, evidence of a kidney transplantation, evidence of dialysis, or two

estimated glomerular filtration rates (eGFR) <30 ml/min/1.73m^2 separated by more than 90 days with no intervening eGFR measurement ≥30 ml/min/1.73m^2 were screened as "positive" for ESRD (N = 822) (Abraham et al., 2014). Of these screened cases, those with medical-record confirmed dialysis, renal transplantation, or arteriovenous fistula (AVF) placement and dialysis were considered "verified" (N=620) (Kitahata et al., 2015; Abraham et al., 2014). Of these 620 verified cases, 601 had a known year of ESRD diagnosis according to the criteria above; these 601 individuals are considered "validated" ESRD cases (Kitahata et al., 2015).

For the purposes of this analysis, only subjects on dialysis – either hemodialysis or peritoneal dialysis – were included. Survival differs significantly between ESRD patients with a kidney transplant compared to those on dialysis, with transplant recipients living longer (United States Renal, 2014). Additionally, only individuals who were validated and diagnosed prior to the cohort-level "ESRD observation window" close date were included in this analysis. Those with a known diagnosis date after observation concluded were excluded. Additionally, when accounting for "late entries," some individuals were lost to follow-up or died before their adjusted time of entry. As a result, the outcome – death – could not be observed for these individuals if it did occur. They were excluded from the analysis. The final analytic sample was comprised of 540 HIV+ adults over 18 years of age with a validated date of ESRD diagnosis.

Outcome

The outcome measure was death. The NA-ACCORD cohorts participating in the ESRD validation procedure contributed information about death through medical records,

the National Death Index, or active study follow-up. For the purposes of this analysis, the month and year of death was utilized. If there was no date of death, the subject was considered to be alive (event-free) and was censored at the end of follow-up.

Risk Factors

Time-Fixed Risk Factors

Race was recorded at entry into each cohort. For the purposes of the risk factor analysis, race was collapsed into two groups: black or other/unknown. In this study sample, "other" groups included white, Hispanic, Asian/Pacific Islander, and multiracial. Because the majority of the study population was black, race was categorized in this way. However, to compare mortality rates in the NA-ACCORD population with those in the general population, race was divided into black, white, and other/unknown. HIV transmission risk was also considered time-fixed for this analysis. Risk groups included: heterosexual contact (including high-risk contact), male-male sexual contact, injection drug use, and other/unknown. "Other" HIV transmission risk groups included hemophiliacs, recipients of blood transfusions, and healthcare or laboratory workers. As the risk for contracting HIV is low in each of these populations, they are grouped together. If individuals belonged to multiple risk groups (for example, heterosexual contact and injection drug use), the behavior that carries a larger risk of HIV transmission was utilized. Cigarette smoking status was considered an "ever versus never" event. Evidence of a smoking diagnosis, self-reported smoking, or notation of smoking in the medical record indicated a history of smoking. Missing smoking status was imputed using multiple imputation.

Hepatitis C and hepatitis B were recorded as time-fixed events if they occurred at any point during NA-ACCORD observation. Hepatitis C was measured as either a positive hepatitis C antibody test, detectable hepatitis C RNA, or the presence of an HCV genotype test. Hepatitis B was measured as a positive hepatitis B surface antigen test, positive hepatitis B E antigen test, or ever having detectable hepatitis B DNA. Commonly, Hepatitis B and C infection precede HIV infection, but individuals are not officially diagnosed until they are linked to care. As a result, the date of diagnosis is likely later than the actual date of infection. For the purposes of this analysis, therefore, a positive Hepatitis C or hepatitis B diagnosis at any point was treated as "positive" for the entire study period. Tenofovir exposure prior to ESRD diagnosis was a time-fixed risk factor measured at study entry. Prior exposure included individuals who were on tenofovir for one month or longer prior to ESRD diagnosis; shorter durations were not considered true "exposures." There have been reports that tenofovir – which is considered widely effective against both HIV and hepatitis B – could have nephrotoxic side effects (Fernandez-Fernandez et al., 2011). It was included in this analysis to further examine the potential relationship between tenofovir, ESRD, and death after ESRD diagnosis.

Time-Varying Risk Factors

Age was defined as the calendar year minus the subject's year of birth. Statin use was defined as the date statins were prescribed. Patients prescribed any of the following medications are considered "statin users": cerivastatin, fluvastatin, lovastatin, prvastatin, rosuvastatin, simvastatin, combination of pravastatin and aspirin, combination of

atorvastatin and amlodipine, combination of ezetimibe and simvastatin, pitavastatin, and a combination of lovastatin and niacin. Diabetes was defined using the date of diagnosis. Diabetes diagnosis date was the earliest date at which one of the following occurred: a measurement of HgA1C >6.5%; a record of prescribed oral hypoglycemic or insulin; one or more ICD-9 codes for diabetes plus treatment with an oral hypoglycemic or insulin; or two random glucose ≥200 mg/dL. Hypertension was defined as the earliest date at which one of the following occurred: a record of prescribed anti-hypertensive medication; or the average of at least 2 systolic blood pressure measurements ≥140 mmHg or diastolic blood pressure measurements ≥90 mmHg over a 1.25 year time window. Patients with a total serum cholesterol >240 mg/dL were considered to have elevated total serum cholesterol. Baseline statin use, diabetes, hypertension, and elevated total serum cholesterol were measured in the window prior to or within nine months after study entry. History of clinical AIDS was defined by the date of first diagnosis of an AIDS-defining illness as outlined by the International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes.

CD4+ cell count was categorized as <200, 200-349, 350-499, or ≥500 cells/μL. CD4+ cell count was measured at study visits, and it was carried forward for a maximum of 1.5 years (18 months) until it was set to "missing." HIV viral load was dichotomized as "detectable versus undetectable" at the level of 200 copies/mL. Like CD4+ cell count, viral load measurements were carried forward for a maximum of 1.5 years before being set to "missing." Baseline CD4+ cell count and viral load were measured in the window of 1.5 years prior to, to 6 months after study entry. ART use was defined as having been on any number of ART drugs in the month.

Missing Data

Risk factor missing data were handled differently depending on the variable. For two conditions, diabetes and elevated total cholesterol, a lack of definition elements measured in an individual was considered evidence of no disease, after taking into account the time periods ("observation windows") in which these elements were measured in each participating cohort. Presumably, patients showing clinical signs of either of these conditions would have been tested for them. The following variables also had missing data: hepatitis C infection, hepatitis B infection, and cigarette smoking. However, the missing data did not exceed 20% for any of these variables, so available case analysis was utilized. Cigarette smoking was imputed using multiple imputation via logistic regression. The data were assumed to be missing at random. The following covariates were used to impute the missing values for cigarette smoking: death, follow-up time, cohort, age at entry, sex, race, HIV transmission risk, CD4+ count at entry, viral load at entry, and ART use. Five imputed datasets were created for this purpose. In this analysis, only one of the five dataset was utilized. Imputed values are not considered missing.

There were no missing data for the outcome. Patients without a death date were considered alive at administrative censoring in December of 2010.

Statistical Analyses

The purpose of this risk factor analysis was to describe and generate hypotheses. As there was no specific exposure of interest, there were no hypothesized confounders. Univariate analyses were conducted using chi-squared tests for proportions to determine

baseline differences in demographic, behavioral, and clinical characteristics between HIV+ individuals with ESRD who died under observation compared to those who did not. The Kruskal-Wallis test was used to determine baseline differences between medians.

Study entry was defined as the month and year of ESRD diagnosis, provided that it occurred during each cohort's ESRD "observation window." Individuals with a diagnosis after the observation window were excluded, as they could no longer be followed up for the event of interest. Those with a diagnosis prior to the observation window and after cohort initiation date were included as "late entries." To account for immortal person-time in which no events could have occurred, study entry for these subjects was the month from ESRD diagnosis. Study exit for each subject was death or censoring on December 31, 2010, two years after the last CD4+ cell or viral load measurement (as a measure of loss-to-follow-up), or 10 years post-ESRD diagnosis – whichever occurred first. Since it was possible that subjects could have missed a number of study visits before returning, they were not considered "lost to follow up" until two years after their last CD4+ cell or viral load measurement. Furthermore, since few individuals survived longer than 10 years post-ESRD diagnosis, data were sparse past this point. As a result, the analysis was restricted to within 10 years post-diagnosis. Individuals surviving longer than this point were censored at 120 months.

Pooled logistic regression models were utilized to explore the crude association between hypothesized risk factors and the outcome, death. Since the data were collected at varying intervals, the smallest of which being at the one-month level, the unit of analysis was person-months. Given this discrete unit of measurement, pooled logistic

regression was the most appropriate method of analysis. Time was parameterized in the model at the month level. Although not all crude associates were statistically significant, all risk factors were included in the final pooled logistic model, as the purpose of this analysis was to generate hypothesis about risk factors. Kaplan-Meier survival curves, stratified by important risk factors for interest, were generated to characterize and visualize survival trends.

Lastly, to compare age-, sex- and race-adjusted mortality rates after ESRD in HIV+ adults in the NA-ACCORD with the general population, publicly available USRDS mortality rates, stratified by these same risk factors, were utilized. Due to the relatively small number of events (deaths) in the NA-ACCORD population, an indirect standardization technique was employed to yield a standardized mortality ratio (SMR). Information from the years 2005 to 2010 was combined to compare rates between the USRDS population and the NA-ACCORD study population, as there was ample information and person-time contributed in these years.

The number of expected deaths was generated for the NA-ACCORD population based on the mortality rates in the general population (per one person-year) multiplied by the person-years at risk in the study population (calculated by dividing the person-months in the analysis by 12). The number of observed deaths was then divided by the number of expected deaths to yield an SMR. An SMR over the value of one suggested that there were more deaths observed in the study population than would be expected given the rates from the general population; an SMR under the value of one suggested the opposite. 95% confidence intervals were calculated to determine if there was a statistically significant difference between the two populations. The upper limit of the confidence

interval was equal to the SMR plus 1.96 multiplied by the square root of the observed number of events divided by the expected number of events. The lower limit was equal to the SMR minus 1.96 multiplied by the square root of the observed number of events divided by the expected number of events.

For the purposes of estimating the SMR, age was adjusted according to age groups specified by the USRDS. Sex was male and female, and race was collapsed into white, black, and other.

Sensitivity Analyses

Although data collection at the month level was considered a discrete time metric, information collection at this level was still relatively precise. Further, the hazard in each person-month was likely reflective of the continuous time hazard rate. Finally, we believed the hazard for death was truly continuous. Therefore, complementary log-log models as well as Cox proportional hazards models (with Efron's method for ties) were run in order to compare results with those from the pooled logistic regression model.

In each of these models, there was an assumption that either the hazard odds or the hazard was constant in each time period. With respect to a specific risk factor, its effect must have been the same throughout all time periods. In order to check that this assumption was not violated with the risk factors included in the model, proportionality was examined using Schoenfeld residuals. Additionally, ln(-lnS(t)) (survival time) curves were plotted versus the ln of analysis time for any risk factor that required further assessment based on the Schoenfeld results. If the two curves remained parallel over follow-up time, the proportional hazards assumption was not violated.

Data management was performed using SAS version 9.3. Data analysis was performed using Stata version 13.1 (SAS Institute; Stata Corp., College Station, Texas, USA).

RESULTS

Analytic Sample

601 ESRD cases were considered validated with a known month and year of diagnosis. Of these patients, two had a kidney transplant; they were removed from the analysis so that the final analytic sample would only include dialysis patients. If the transplant patients were included in the analysis, the results could have been biased, as individuals with kidney transplants are expected to live longer than those on dialysis. Additionally, subjects from one cohort with missing comorbidities data were excluded, bringing the sample from 599 to 595 patients. Since several of the risk factors for death in this analysis were comorbid conditions, patients lacking all comorbidity information did not contribute.

Of these 595 remaining patients, 25 were diagnosed with ESRD after their cohort-level ESRD observation window closed. They were excluded from the analysis. Patients diagnosed before the observation window began were included as late-entries, and their entry time depended on how long before their cohort-level observation window they were diagnosed. After adjusting for late entry, some patients did not enter the study until 10 years after ESRD diagnosis. Since data were sparse after 10 years post-diagnosis, follow-up time was stopped at this point. Subjects entering after 120 months, therefore, were excluded, bringing the sample from 570 to 567. Lastly, after accounting for late entry, 27 individuals either died or were lost to follow-up before their adjusted entry. The final analytic sample included 540 HIV+ adults diagnosed with ESRD. Figure 1 describes the selection into the study population.

Baseline Characteristics of HIV+ Adults with ESRD

Demographic Characteristics (Table 1)

A total of 540 HIV+ adults aged 18 to 89 years old contributed 23,491 person-months, or 1958 person-years, to this analysis. The median time contributed was 30 months, or 2.5 years (IQR = 14 to 56 months; 1.17 to 4.67 years). A total of 255 participants (47.2% of the study sample) died under follow-up. Characteristics of participants can be viewed in Table 1. The median age at ESRD diagnosis was 44 (IQR = 38, 51), and this age did not differ by survival (age 45 [IQR = 38 to 51] for survivors compared to age 43 [IQR = 36 to 50] for those who died, p = 0.05). There was no statistically significant difference by sex at baseline; 31% of those who died were female, and 28% who survived were female (p = 0.45). However, there was a significant difference between these groups with respect to race: participants who died were more likely to be black; 91% of those who died and 80% of those who survived were black (p = <0.001). Additionally, there was a significant difference in HIV transmission risk group between those who died and those who survived, with patients who survived more likely to report belonging to the risk group "men who have sex with men" (18% who died compared to 29% who survived, p = 0.03).

Clinical and HIV-Specific Characteristics (Table 1)

HIV+ ESRD patients who died were more likely to have a history of cigarette smoking, with 77% of those who died indicating ever having smoked, compared to 63% of those who remained alive (p = 0.001). People who died were also more likely to have had a history of AIDS; 49% who died had been diagnosed with AIDS compared to 33%

who survived (p = <0.001). Individuals with a history of statin use were more likely to remain alive than those reporting no statin use (9% of those who died and 20% of those who survived, p = <0.001). Those who remained alive were also more likely to have a history of hypertension, at 62% compared to 40% among those who died (p = <0.001). ESRD patients who died under follow-up were statistically significantly more likely to have a low CD4+ cell count, a detectable viral load, and not be on an ART regimen (Table 1).

Survival After ESRD Diagnosis

Figure 3, Figure 4, Figure 5, and Figure 6 are Kaplan-Meier survival curves estimating the survival experience of the HIV+ population with ESRD in NA-ACCORD. Figure 3 represents the overall survival estimate. Based on this curve, the median survival post-ESRD diagnosis was approximately five years, or 60 months. Figure 4 is the survival estimate, stratified by race. As the graph demonstrates, the median survival for black subjects was close to the overall median survival, at approximately 60 months. The median survival for "other" race, however, was significantly better, although the exact estimate could not be determined due to sparse data. The log-rank test for equality of survivor functions had a p-value of 0.005, confirming that the survival experience between the races was significantly different.

Figure 5 is the Kaplan-Meier curve for survival, stratified by sex. The curves were consistently close to each other throughout follow-up time, with the median survival for both males and females approximately 60 months. The log-rank p-value suggested that there was no difference by sex in terms of survival (p = 0.33). Figure 6 displays the

survival curves by baseline age of study participants. Survival appeared best for those between the ages of 50 and 59 in the first 60 months, but past 60 months, the curves for all age groups appeared similar. The log-rank test suggested there was no difference in survival among these baseline age groups ($p = 0.63$).

Hazard by Month

Figure 2 represents a visualization of the observed hazard by month from ESRD diagnosis in this population. At each month from diagnosis, the number of deaths was divided by the number of patients at risk and plotted. Until month 120, in which the data were sparse and surviving subjects were censored, the hazard appeared relatively stable over time. The hazard was slightly elevated in the first one or two years -- until approximately 30 months. The hazard decreased at approximately year five, month 60. Overall, the hazard was small in each month.

Risk Factors for Death: Results from Univariate Analyses

The univariate relationships between hypothesized risk factors for death and the outcome are presented in Table 2. Age and sex were not statistically significantly associated with death in the univariate models. “Other” race, including white, Hispanic, Asian/Pacific Islander, and multiracial, was associated with a reduced hazard of death (HOR: 0.55, 95% CI: (0.36, 0.84). Men who have sex with men was the only HIV transmission risk group to have a statistically significant relationship with death. The hazard odds ratio of death in this group was 0.66 (95% CI: 0.47, 0.94), suggesting that

men who have sex with men had lower hazard odds of dying than the reference group in this population – those with an HIV transmission risk of heterosexual contact.

Hepatitis C, hepatitis B, diabetes, and elevated total cholesterol did not have a statistically significant association with death in the univariate models. The hazard odds of death among cigarette smokers, however, were nearly 50% higher compared to those who do not smoke (HOR: 1.48, 95% CI: 1.02, 2.15). Hypertension and history of statin use were both protective of death, with hazard odds ratios of 0.67 and 0.61, respectively (95% CIs: 0.52, 0.86; 0.41, 0.91). The hazard odds of death among subjects with a history of clinical AIDS were 2.63 times higher than those without AIDS (95% CI: 2.03, 3.41).

As CD4+ cell count increased, the hazard of death decreased. There was a statistically significant reduction in hazard odds with each increasing CD4+ cell count group in the univariate analyses. The hazard odds of death in the highest CD4+ cell group (≥500 cells//μl) was approximately 70% times lower than in the lowest group (<200 cells/ μl) (HOR: 0.34, 95% CI: (0.21, 0.55). Subjects with a detectable viral load had over three times the hazard odds of death compared to those who were virally suppressed at the level of 200 copies/mL (HOR: 3.38, 95% CI: 2.38, 4.80). Patients on ART therapy had a 75% reduction in hazard odds of death compared to those not on ART (HOR: 0.15, 95% CI: 0.11, 0.21). Prior tenofovir exposure was not significantly associated with death in the univariate analyses.

Risk Factors for Death: Results from Multivariate Analysis

Results from the multivariate pooled logistic analysis are displayed in Table 2. Nearly all hypothesized risk factors for death among HIV+ ESRD patients were included

in the final model. As anticipated, not all risk factors were statistically significantly associated with death in the unadjusted models. However, the goal of this analysis was to generate hypotheses about potential risk factors; therefore, including the full model seemed appropriate, despite the level of significance in the univariate associations. HIV transmission risk group was the only original risk factor not included in the final model, as injection drug use, one of the risk behaviors, was considered to be collinear with hepatitis C infection.

Death had a "U-shaped" relationship with age in this analysis. Patients under the age of 40 seemingly had higher hazard odds of death than those aged 40-49, which was the reference group. Ultimately, however, this association was not statistically significant. Patients 60 years or older had a two times higher hazard of death at all time points compared to patients aged 40-49, and this increased hazard was significant (HOR: 2.29, 95% CI: 1.29, 4.07). Sex and race were not predictive of death in this population. Of the comorbid conditions assessed, only elevated total cholesterol (>240 mg/dL) and hypertension were significantly associated with death. Patients with elevated total cholesterol had approximately 50% increased hazard odds of death compared to those with normal cholesterol levels (HOR: 1.57, 95% CI: 1.13, 2.19). Those with hypertension had nearly 30% decreased hazard odds of death compared to those without hypertension (HOR: 0.70, 95% CI: 0.49, 0.99). A history of clinical AIDS diagnosis increased the hazard odds of death by over two-fold, with a hazard odds ratio of 2.41 (95% CI: 1.69, 3.45). Patients in the highest CD4+ cell group had 50% reduced hazard odds of death compared to those in the lowest CD4+ cell group, but the groups in between were not statistically significantly associated with lower hazard (HOR: 0.46, 95% CI: 0.25, 0.85).

Patients not on ART therapy had over 75% higher hazard odds of death compared to those not on ART therapy (HOR: 0.12, 95% CI: 0.08, 0.19). The hazard odds ratio for individuals exposed to tenofovir before ESRD diagnosis compared to those without this exposure was 1.71 (95% CI: 1.09, 2.70).

In general, some factors that were significantly associated with death in the univariate analyses were not associated in the final pooled logistic model, and vice versa. Being in the oldest age group (60 years or older), having elevated total cholesterol, and prior tenofovir exposure were associated with death in the multivariate model, but not in the univariate model. Non-black race, cigarette smoking, hypertension, and certain CD4+ groups were associated only in the univariate analyses.

Risk Factors for Death: Results from the Sensitivity Analyses

A complementary log-log model and Cox proportional hazards model were both run to compare results from the pooled logistic model. The results from the complementary log-log model are displayed in Table 3. As expected due to the small (< 0.50) hazard in each person-month, the unadjusted and adjusted estimates in Table 3 were almost identical to those from the univariate and multivariate pooled logistic model in Table 2. The largest change in estimate was less than one whole digit. The results from the Cox proportional hazards model are displayed in Table 4. Again, the results from this model were virtually the same as the other two models.

To assess whether the proportional hazards assumption was violated, in the Cox model, ln(-lnS(t)) (survival time) curves were plotted for each risk factor versus the ln of

analysis time. In all cases, the difference between the curves was relatively parallel, suggesting that the assumption was not violated.

Standardized Mortality Ratios

In order to compare mortality rates after ESRD diagnosis in the NA-ACCORD population to those in the general U.S. population, age-, sex-, and race-adjusted standardized mortality ratios (SMR) were calculated for the years 2005 through 2010, combined.

The SMR, after adjusting for age, was 1.09, which suggests that the number of observed deaths was approximately the same as would be expected if HIV+ adults with ESRD had the same probability of dying as the general population with ESRD, after accounting for age (95% CI: 0.89, 1.29) (Table 5). The sex-adjusted SMR was 0.59, with a 95% confidence interval of 0.48 to 0.70. The interpretation of this SMR is that the number of observed deaths was fewer than would be expected if the HIV+ adults with ESRD had the same probability of dying as the general population with ESRD (Table 6). Here, however, there was no adjustment for age. Lastly, the race-specific SMR was 0.66, with a 95% CI of 0.52 to 0.79 (Table 7). Again, the interpretation suggests that the number of observed deaths in the NA-ACCORD population was lower than expected based on USRDS data. This SMR, like the sex-adjusted, also did not account for age. We were unable to adjust for age, sex, and race simultaneously because the mortality rates for each stratum of these three risk factors were not available from USRDS.

DISCUSSION

This analysis sought to address several questions with respect to renal complications in PLWH. First, utilizing data from verified cases of ESRD in the NA-ACCORD cohort, this analysis identified risk factors for death among HIV+ adults diagnosed with ESRD. These same data were used to characterize survival after diagnosis, stratified by important demographic factors. Second, this study compared age-, sex-, and race-adjusted mortality rates after ESRD diagnosis in the NA-ACCORD with those in the general population based on USRDS estimates. The resulting calculations, the standardized mortality ratios, described the mortality experience of HIV+ patients with ESRD compared to that of the general population with ESRD.

Risk Factors for Death

Overall, the results from the primary analysis – the pooled logistic model – were nearly identical to those from the complementary log-log and Cox proportional hazards models examined as sensitivity analyses. The results from the pooled logistic regression were interpreted as hazard odds ratios, and the results from the other models were interpreted as hazard ratios. Because the discrete time period was so small in the pooled logistic model, however, the hazard was also small in each time period (Figure 2). For this reason, the hazard odds ratios approximated the hazard ratios. Throughout the discussion, therefore, the term "hazard" rather than "hazard odds" will be utilized.

Adjusted results from the regression models identified the risk factors associated with death in the HIV+ sample with ESRD. Demographically, only subjects in the oldest age group, over 60 years old, had a significant increased hazard of death compared to the

reference group of 40-49 years. This result was not surprising given that this group had no upper bound, and increasing age increases the risk of death in general. The 40 years and below category came close to statistical significance, which was also not surprising, since there were relatively few subjects with ESRD at this comparatively early age. Perhaps HIV+ patients under the age of 40 who develop ESRD have worse overall health than their peers, which could dictate why they experience this condition early. This poor health might also account for their increased hazard of death after ESRD diagnosis.

There was no significant racial difference with respect to progression to death in the multivariate analysis. Previous studies, both in HIV-infected and uninfected individuals, suggest that the black population experiences a higher burden of ESRD. Whether this population is also at an increased risk for death post-diagnosis is unclear, particularly since this NA-ACCORD study sample is 85% black. In this case, the lack of significance could have been due to the composition of the study population; there were relatively few subjects of other races, and even fewer outcomes observed in these populations. Future analyses with different study populations may elucidate the relationship between race and risk of death after diagnosis.

Of the traditional risk factors for developing ESRD, only elevated total cholesterol and hypertension were significant risk factors for death in this population. There is evidence to suggest that hepatitis C, hepatitis B, and smoking increase the risk of developing ESRD; however, none is associated with increased hazard of death in this analysis (Lee et al., 2014; Chen et al., 2014). Although literature examining risk factors for death after ESRD diagnosis in both the HIV+ and uninfected population is relatively sparse, diabetes has been found to be associated with both the risk of developing and the

risk of dying from ESRD (Lowrie & Lew, 1990). Nevertheless, diabetes exhibits no relationship with death in the NA-ACCORD population. Overall, however, relatively few individuals were diagnosed with hepatitis B and diabetes in this population, which could explain the lack of association.

Hypertension's protective effect against death was only marginally significant, with an upper 95% CI limit of 0.99. Hypertension is one of the most prominent risk factors for ESRD; however, there is no previous evidence or biological rationale to suggest that it would reduce the hazard of death after ESRD diagnosis. In the NA-ACCORD sample, patients were considered hypertensive if they had a record of prescribed anti-hypertensive medication. Based on this criterion, it seems possible that the small protective effect demonstrated in the model could be related to linkage to care. Patients who were classified as hypertensive in this sample may be largely the same patients who were in care and managing their comorbid conditions. Perhaps individuals in this sample who were not classified as hypertensive are those who had unmanaged hypertension. If this was the case, then hypertension might look protective because those diagnosed are those linked to care.

In general, HIV-specific risk factors were more strongly associated with the risk of death in this population compared to the comorbidities described above. A clinical history of AIDS doubled the hazard of death after ESRD diagnosis, after adjusting for other HIV-specific factors such as CD4+ cell count, HIV viral load, and ART therapy. There are several potential explanations for this increased risk. Firstly, it is possible that the subjects diagnosed with AIDS were those who had been infected with HIV longer. These adults were more likely to have increased damage to their immune system, which

could have translated into worse outcomes after being diagnosed with a comorbid condition such as ESRD. Furthermore, patients diagnosed with AIDS in a time in which potent antiretroviral therapy was available might be patients who were not connected to care for several reasons. In general, those not connected to care are more likely to have a myriad of negative health conditions – some of which may not have been captured or adjusted for in this analysis.

Those with a CD4+ cell count above 500 cells/μl had a reduced hazard of death after ESRD diagnosis compared to those with a count below 200 cells/μl. Patients with CD4+ counts above 200 and below 500 cells/μl, however, did not have a statistically significant difference in risk compared to the lowest group in this analysis. Overall, patients with a high CD4+ count were likely to be patients with well-managed HIV and well-managed health in general. Their immune systems were likely stronger, and their overall health was likely better, which could have accounted for their reduced risk of death from ESRD. Individuals with an undetectable viral load at the level of less than 200 copies/mL were similarly at a reduced risk of death; the reason was presumably similar to that for CD4+ cell count. The cutoff of 200 copies/mL is relatively stringent, provided that various cutoffs are used in the literature, with up to 500 copies/mL deemed "undetectable." Particularly with this stringent cutoff, those with an undetectable viral load in this sample were likely adherent to their drug regimen and had well-managed HIV.

Individuals not on ART therapy had over a 75% higher hazard of death than those not on ART therapy. This association likely reflects the fact that patients not on ART are not managing their HIV and overall health as well as those on a regimen. As with CD4+

cell count and viral load, patients not on ART might not be connected to care, may be homeless, may abuse drugs or alcohol, may have mental illnesses, or may have adherence issues, amongst other potential economic or social barriers that contribute to poorer health outcomes in general. These factors were not directly included in this analysis; it is possible that ART therapy captured some of these possibilities and helped explain the high hazard of death among this group.

Lastly, tenofovir exposure for at least one month prior to ESRD was associated with an increased hazard of death among patients with HIV and ESRD in this analysis. This risk factor was included in the model because of its potential nephrotoxic side effects. There is limited and conflicting literature examining the effect of tenofovir on patients with failing kidneys, with some suggesting that increased tenofovir exposure results in increased risk of developing chronic kidney disease (Mocroft et al., 2010). In this analysis, tenofovir was also associated with increased risk once one is already diagnosed with ESRD. Because there is limited literature examining this association to date, however, further research is necessary to clarify this association. Nevertheless, after adjusting for demographic, traditional, and HIV-specific risk factors, tenofovir increased the hazard of death in this population by nearly 70%, which could underscore its nephrotoxic effects, even post ESRD diagnosis.

Survival After ESRD Diagnosis

The Kaplan-Meier curves stratified by sex, race, and baseline age are shown in Figures 3 to 6. Overall, the median survival for HIV+ adults on dialysis post-ESRD diagnosis was five years. According to the most recent USRDS data, among patients

starting dialysis in 2007, approximately 45% are expected to survive for 5 years (United States Renal, 2014). Given these numbers, it appears that the HIV+ sample has similar or potentially marginally better survival estimates post-diagnosis. However, it is important to note that the average age at diagnosis in the NA-ACCORD sample was 44, whereas the average age in the general population, according to USRDS data, is closer to 60 or 65. Given these different age distributions, it is critical to age-adjust and then examine mortality, a calculation that will be discussed later.

As the Kaplan-Meier curves and previously discussed log-rank tests suggest, there was seemingly a statistically significant difference in survival between the black and non-black populations in this sample, with the former having worse survival estimates. Again, there is an abundance of evidence to suggest that blacks are more at risk for developing ESRD; their survival post-diagnosis is not as clear. One limitation of this sample is that there were relatively few patients of "other" race contributing information past five years post-ESRD diagnosis. For this reason, the comparison between survival stratified by race should be analyzed with caution. Similarly, there appeared to be no significant difference in the survival of men and women post-ESRD; however, this sample consisted of twice as many males as females. It is possible that the uneven distribution of sex could have obscured the relationship between the sexes with respect to survival.

Standardized Mortality Ratios

In order to adjust for the different age distributions of the USRDS population and the NA-ACCORD population, an age-adjusted standardized mortality ratio was calculated based on data from years 2005 to 2010. The results of this calculation suggest

that the number of observed deaths in the NA-ACCORD population was approximately what would be expected if HIV+ adults with ESRD had the same probability of dying as the general population with ESRD.

It is important to emphasize that the sex- and race-adjusted SMRs were also calculated, and they were both below one. However, they are not adjusted for age. The difference in mean age at ESRD diagnosis in the NA-ACCORD population compared to the general population is between 15 and 20 years. Given this significant difference, the most important adjustment is arguably age. Since there are no publicly available USRDS mortality rates adjusting for sex, age, and race combined, the comparison between the general population and NA-ACCORD population based on these three factors cannot be made at the current time. Given these limitations and the distinct age distributions of the two populations, the age-adjusted SMR seems the most appropriate from which to draw conclusions, and it appears that the observed deaths in the NA-ACCORD population is in keeping with what would be expected based on data from the general population.

In summary, the results of this analysis identified some risk factors for death among HIV+ adults with ESRD, characterized survival post-diagnosis, and compared survival to that of the general U.S. population. Overall, HIV-specific risk factors were more strongly associated with the risk of death than traditional risk factors for ESRD in this population. The median survival post-diagnosis was approximately five years, though the average age of diagnosis was younger than that of the general population, at 44 years compared to 60 to 65 years. Lastly, after adjusting for age, the number of deaths observed in the NA-ACCORD population was approximately what would be expected based on the age-specific mortality rates in the general population.

Strengths and Limitations

This analysis has some limitations that could potentially be addressed in future studies. Perhaps the most significant limitation is the sample size of 540, with the majority of cases being male and of black race. This sample size is reflective of the intensive screening and verification process for ESRD cases; only those with a known month and date of ESRD diagnosis were included. The demographic composition – particularly with respect to race – likely reflects the elevated risk of ERSD among particular groups. Nevertheless, the limited female subjects and those from other races render comparisons among these groups more difficult. Further studies with more subjects, events, and demographic diversity might be able to supplement the findings presented here. Furthermore, although exposure ascertainment is relatively complete, there were some traditional risk factors for which there was limited data. As was mentioned previously, relatively few patients were diagnosed with diabetes and hepatitis B in this sample. Again, a larger sample might capture more patients with these conditions and clarify the association between them and the risk of death from ESRD.

Although this analysis demonstrated that HIV-related risk factors were more strongly associated with the risk of death compared to traditional age-related comorbidities, there was one HIV-specific variable that was not able to be assessed: time since seroconversion. Quantifying the time from HIV infection could be important to better understand the risk of death among HIV+ ESRD patients. Those infected with HIV for longer periods of time presumably have a different health profile than those recently

infected. Still, in this sample, the date of AIDS diagnosis was available, which provides some insight into how long a particular patient might have been infected.

This analysis has several important strengths. Notably, it contributes to the growing field of research on aging and HIV. With a steadily increasing proportion of HIV+ adults over the age of 50, research on age-related conditions in this population is becoming imperative. This analysis seeks to further explore the relationship between one important condition of aging – ESRD – and HIV. Previous research has determined that the risk of certain conditions of aging is higher among HIV+ individuals; this analysis seeks to characterize the trajectory of one such condition.

The data used from this analysis are representative of HIV+ patients connected to care in North America. All cases of ESRD have been thoroughly screened and verified, with a specific date of diagnosis to the month level. Overall, the cohorts that contribute data to NA-ACCORD and to this analysis have comprehensive data collection procedures, so there is an abundance of demographic, behavioral, and clinical information available for analysis. For the purposes of this study, data were updated at the month level; the time-varying nature of many risk factors is therefore captured in detail. Moreover, the USRDS data provide a valuable reference group from which to draw comparisons in this analysis. It is critical to conduct analyses on only the HIV+ NA-ACCORD population in some instances. In order to identify risk factors for death among this population, for example, no reference group is needed. However, to evaluate the overall affect that HIV might have on the aging process, this reference group is crucial.

Implications and Future Research

This analysis supplements existing literature examining the relationship between conditions associated with aging and HIV. Many previous studies have found that survival among HIV+ adults with ERSD has been improving with time and accompanying advancements in HIV management, though the magnitude of this improvement may vary by population (Ahuja et al, 2002; Rodriguez et al., 2003; Atta et al., 2007). The median survival estimate post-ERSD diagnosis in this NA-ACCORD population is approximately 5 years, which is higher than the results of the previous studies and comparable to that of the general ESRD population on dialysis. Since improvements are expected with time, the results of this study are in keeping with what one might expect based on previous literature. Future research should continue to examine this trend and identify factors associated with survival.

Importantly, the median age at diagnosis in this study population is between 15 to 20 years younger than in the general population. There has been conflicting literature about the timing of age-related conditions in HIV+ adults, including ESRD, with some literature suggesting that ESRD occurs as earlier ages among HIV+ adults, and some suggesting that it occurs at the same time as in the general population (Althoff et al., 2015; Abraham et al, 2014; Rodriguez et al., 2003). Future studies might continue to contribute to this discussion, as the implications for screening and treatment could differ based on age at diagnosis.

Clinically, the results of this study have identified HIV-specific risk factors as being more strongly associated with the risk of death from ESRD than traditional age-associated conditions. This finding emphasizes the continued management of HIV in

aging adults, especially with respect to treatment. Certainly, more research should be done to clarify the association between other comorbid conditions and the risk of death from ERSD, as the limitations of this analysis could have obscured an association if it exists. However, these results did identify elevated total cholesterol as an important target for intervention, as patients with this condition are at an increased risk of death post-diagnosis. Overall, these risk factors should be addressed as priorities among HIV+ adults diagnosed with ESRD.

The timing of ESRD diagnosis and overall survival post-diagnosis in this population also has important clinical considerations. The earlier age at diagnosis might prompt earlier screening in the HIV+ aging population. Nevertheless, it is encouraging that the expected survival in the NA-ACCORD population on dialysis is similar to that of the general population, once diagnosed with ERSD. Survival among HIV+ patients looks significantly better if these patients are on a form of ART treatment, have high CD4+ cell counts, and have undetectable HIV viral loads. Well-managed HIV seems particularly critical for managing ESRD in this population. In general, characterizing the experience of HIV+ adults with comorbid conditions such as ESRD is imperative to better understand the experience of aging with HIV in the modern era.

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TABLES AND FIGURES

Figure 1. Flowchart of Selection into the Study Population

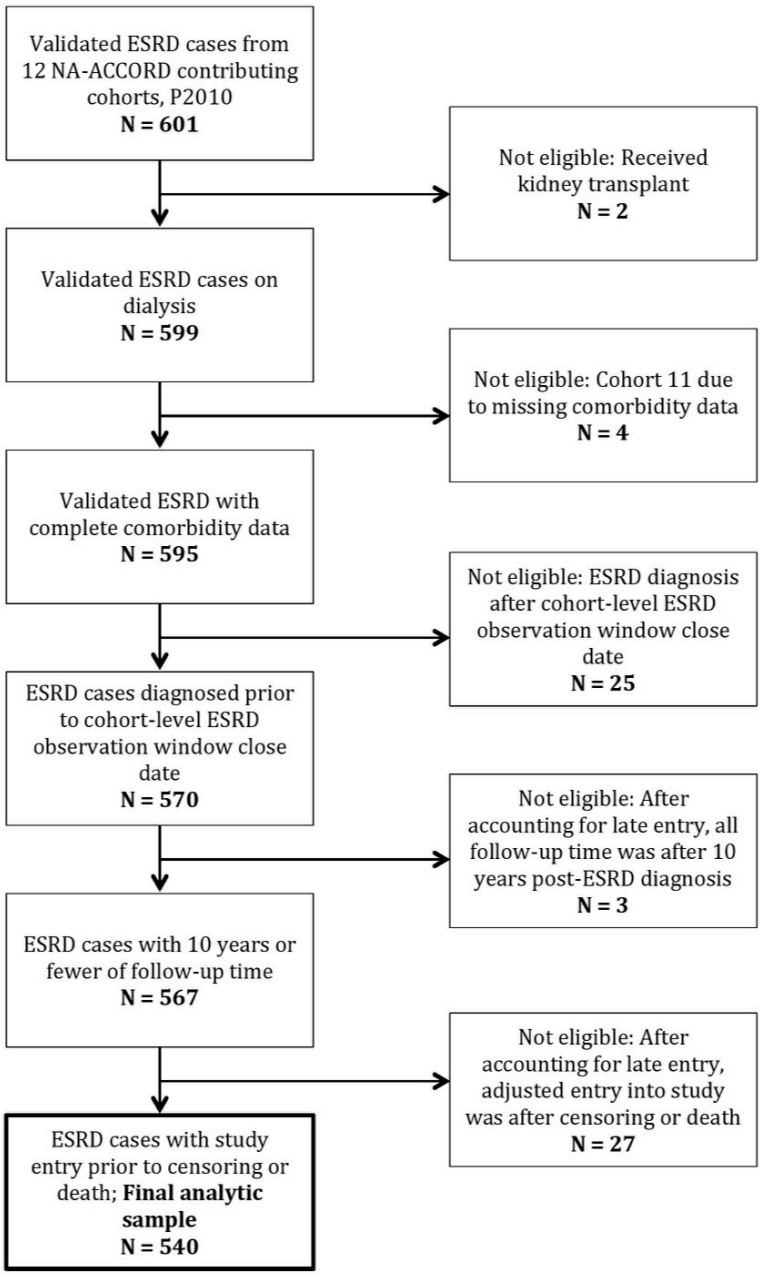


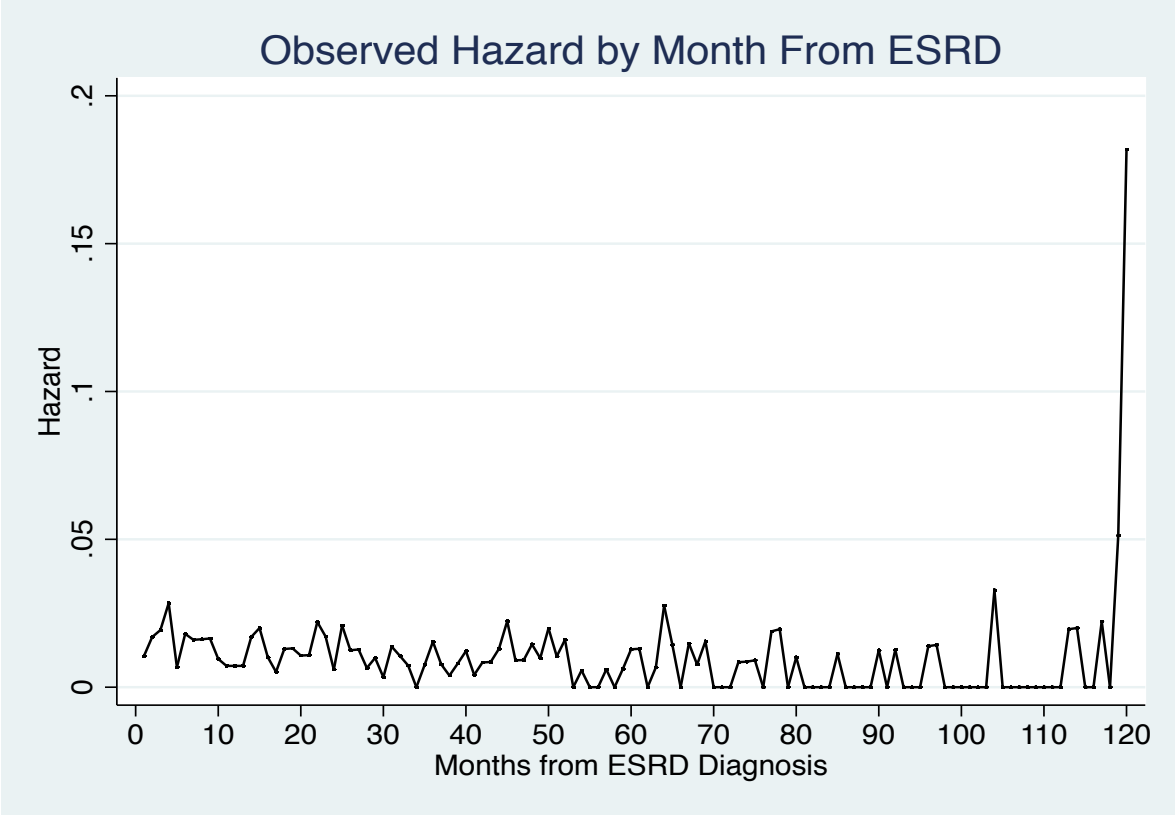
Table 1. Characteristics of HIV+ Adults at ESRD diagnosis in NA- ACCORD

Characteristics	Dead N= 255		Alive N = 285		P-value
	n	%	n	%	
Age (median, IQR)	43	(36-50)	45	(38-51)	0.12
Age group					0.21
<40 years	94	37%	83	29%	
40-49 years	95	37%	110	39%	
50-59 years	51	20%	73	26%	
≥60+ years	15	6%	19	7%	
Female	80	31%	81	28%	0.45
Race/Ethnicity					**<0.001**
Black	231	91%	227	80%	
Non-Black	24	9%	58	20%	
HIV transmission risk					**0.03**
MSM	47	18%	82	29%	
Heterosexual	114	45%	110	39%	
IDU	69	27%	61	21%	
Other/Unknown	25	10%	32	11%	
Hepatitis C infection	92	36%	95	33%	**0.03**
Missing	44	17%	30	11%	
Hepatitis B infection	23	9%	28	10%	0.76
Missing	25	10%	23	8%	
Observed Cigarette Smoking	137	54%	145	51%	**0.001**
Imputed values	59	23%	34	12%	
Missing	26	10%	54	19%	
Diabetes	37	15%	61	21%	**0.04**
Hypertension	103	40%	178	62%	**<0.001**
Elevated total cholesterol (> 240 mg/dL)	91	36%	95	33%	0.57
Statin prescription	22	9%	56	20%	**<0.001**
History of clinical AIDS	126	49%	93	33%	**<0.001**
CD4+ count (cells/µl)					**<0.001**
<200	127	50%	95	33%	
200-349	53	21%	53	19%	
350-499	36	14%	52	18%	
≥500	15	6%	40	14%	
Missing	24	9%	45	16%	
Detectable HIV RNA (≥200 copies/mL)	185	73%	152	53%	**<0.001**
Missing	39	15%	50	18%	

ART Use	107	42%	154	54%	**0.005**
Prior tenofovir prescription	38	15%	46	16%	0.69

Bold signifies statistical significance (p-value <0.05)
P-values were estimated using chi square test statistics for a difference in proportions and the Kruskal Wallis test statistic for a difference in medians
Abbreviations: MSM = men who have sex with men; IDU = injection drug users; ART = antiretroviral therapy

Figure 2. Observed Hazard by Month from ESRD Diagnosis in NA-ACCORD



Hazard was calculated by dividing the number of events in each month by the number at risk in each month after ESRD diagnosis

Table 2. Pooled logistic regression: Crude and adjusted hazard odds ratios for the risk of death in HIV+ ESRD patients in NA-ACCORD

Characteristics	HOR	95% CI	aHOR	95% CI
Age				
<40 years	1.14	0.84, 1.55	1.44	0.97, 2.13
40-49 years (ref)	1.00	--	1.00	--
50-59 years	0.87	0.63, 1.21	1.15	0.75, 1.76
≥60 years	1.18	0.76, 1.83	**2.29**	**1.29, 4.07**
Sex				
Male	1.00	--	1.00	--
Female	1.14	0.87, 1.49	1.25	0.90, 1.75
Race/Ethnicity				
Black (ref)	1.00	--	1.00	--
Non-Black	**0.55**	**0.36, 0.84**	0.97	0.57, 1.68
HIV transmission risk				
Men who have sex with men	**0.66**	**0.47, 0.94**	--	--
Heterosexual (ref)	1.00	--	--	--
Injection drug users	1.12	0.82, 1.51	--	--
Other/Unknown	0.89	0.57, 1.38	--	--
Hepatitis C infection	1.24	0.94, 1.64	0.97	0.68, 1.39
Hepatitis B infection	0.99	0.64, 1.53	0.98	0.57, 1.68
Cigarette smoking	**1.48**	**1.02, 2.15**	1.24	0.81, 1.91
Diabetes	0.90	0.64, 1.25	0.92	0.59, 1.44
Hypertension	**0.67**	**0.52, 0.86**	**0.70**	**0.49, 0.99**
Elevated total cholesterol	1.21	0.93, 1.56	**1.57**	**1.13, 2.19**
Statin prescription	**0.61**	**0.41, 0.91**	0.69	0.39, 1.20
History of clinical AIDS	**2.63**	**2.03, 3.41**	**2.41**	**1.69, 3.45**
CD4 count (cells/µl)				
<200 (ref)	1.00	--	1.00	--
200-349	**0.63**	**0.45, 0.88**	0.83	0.55, 1.25
350-499	**0.55**	**0.40, 0.82**	0.80	0.50, 1.30
≥500	**0.34**	**0.21, 0.55**	**0.46**	**0.25, 0.85**
Detectable HIV RNA	**3.38**	**2.38, 4.80**	**1.82**	**1.18, 2.80**
ART Use	**0.15**	**0.11, 0.21**	**0.12**	**0.08, 0.19**
Prior tenofovir prescription	1.27	0.89, 1.81	**1.71**	**1.09, 2.70**

Bold signifies statistical significance (p-value <0.05)
Adjusted models included all variables seen in the table and NA-ACCORD cohort

Table 3. Complementary log-log regression: Crude and adjusted hazard ratios for the risk of death in HIV+ ESRD patients in NA-ACCORD

Characteristics	HR	95% CI	aHR	95% CI
Age				
<40 years	1.13	0.84, 1.54	1.42	0.98, 2.09
40-49 years (ref)	1.00	--	1.00	--
50-59 years	0.87	0.63, 1.21	1.14	0.75, 1.73
≥60 years	1.18	0.76, 1.82	**2.25**	**1.29, 3.93**
Sex				
Male	1.00	--	1.00	--
Female	1.14	0.87, 1.48	1.25	0.91, 1.74
Race/Ethnicity				
Black (ref)	1.00	--	1.00	--
Non-Black	**0.55**	**0.36, 0.84**	0.99	0.58, 1.68
HIV transmission risk				
Men who have sex with men	**0.66**	**0.47, 0.94**	--	--
Heterosexual (ref)	1.00	--	--	--
Injection drug users	1.11	0.83, 1.50	--	--
Other/Unknown	0.89	0.58, 1.38	--	--
Hepatitis C infection	1.24	0.94, 1.63	0.98	0.69, 1.39
Hepatitis B infection	0.99	0.64, 1.53	0.96	0.57, 1.63
Cigarette smoking	**1.48**	**1.02, 2.13**	1.23	0.81, 1.86
Diabetes	0.90	0.65, 1.25	0.93	0.60, 1.44
Hypertension	**0.67**	**0.52, 0.87**	**0.70**	**0.50, 0.98**
Elevated total cholesterol	1.20	0.94, 1.55	**1.55**	**1.13, 2.14**
Statin prescription	**0.61**	**0.41, 0.91**	0.69	0.40, 1.20
History of clinical AIDS	**2.59**	**2.01, 3.35**	**2.37**	**1.67, 3.36**
CD4 count (cells/µl)				
<200 (ref)	1.00	--	1.00	--
200-349	**0.64**	**0.46, 0.88**	0.83	0.56, 1.25
350-499	**0.56**	**0.37, 0.82**	0.81	0.51, 1.29
≥500	**0.34**	**0.21, 0.55**	**0.47**	**0.26, 0.85**
Detectable HIV RNA	**3.34**	**2.36, 4.72**	**1.81**	**1.18, 2.76**
ART Use	**0.15**	**0.10, 0.22**	**0.13**	**0.08, 0.20**
Prior tenofovir prescription	1.27	0.89, 1.80	**1.70**	**1.09, 2.66**

Bold signifies statistical significance (p-value <0.05)
Adjusted models included all variables seen in the table and NA-ACCORD cohort

Table 4. Cox proportional hazards regression: Crude and adjusted hazard ratios of for the risk of death in HIV+ ESRD patients in NA-ACCORD

Characteristics	HR	95% CI	aHR	95% CI
Age				
<40 years	1.13	0.84, 1.54	1.42	0.97, 2.08
40-49 years (ref)	1.00	--	1.00	--
50-59 years	0.87	0.63, 1.21	1.14	0.75, 1.73
≥60 years	1.18	0.76, 1.82	**2.22**	**1.27, 3.88**
Sex				
Male	1.00	--	1.00	--
Female	1.14	0.87, 1.48	1.25	0.90, 1.73
Race/Ethnicity				
Black (ref)	1.00	--	1.00	--
Non-Black	**0.55**	**0.36, 0.84**	0.98	0.58, 1.68
HIV transmission risk				
Men who have sex with men	**0.67**	**0.48, 0.94**	--	--
Heterosexual (ref)	1.00	--	--	--
Injection drug users	1.11	0.83, 1.50	--	--
Other/Unknown	0.89	0.58, 1.38	--	--
Hepatitis C infection	1.24	0.95, 1.63	0.98	0.69, 1.38
Hepatitis B infection	0.99	0.64, 1.52	0.97	0.57, 1.63
Cigarette smoking	**1.47**	**1.01, 2.13**	1.23	0.81, 1.87
Diabetes	0.90	0.65, 1.25	0.93	0.60, 1.44
Hypertension	**0.67**	**0.52, 0.87**	**0.70**	**0.50, 0.99**
Elevated total cholesterol	1.20	0.94, 1.55	**1.55**	**1.13, 2.13**
Statin prescription	**0.61**	**0.41, 0.91**	0.69	0.40, 1.20
History of clinical AIDS	**2.59**	**2.00, 3.35**	**2.35**	**1.66, 3.34**
CD4 count (cells/µl)				
<200 (ref)	1.00	--	1.00	--
200-349	**0.64**	**0.46, 0.88**	0.83	0.55, 1.24
350-499	**0.56**	**0.37, 0.83**	0.81	0.51, 1.29
≥500	**0.34**	**0.21, 0.55**	**0.47**	**0.26, 0.86**
Detectable HIV RNA	**3.32**	**2.35, 4.70**	**1.79**	**1.17, 2.73**
ART Use	**0.15**	**0.11, 0.22**	**0.13**	**0.08, 0.20**
Prior tenofovir prescription	1.27	0.89, 1.80	**1.69**	**1.08, 2.63**

Bold signifies statistical significance (p-value <0.05)
Adjusted models included all variables seen in the table and NA-ACCORD cohort

Figure 3. Kaplan-Meier Survival Estimate of HIV+ ESRD patients in NA-ACCORD

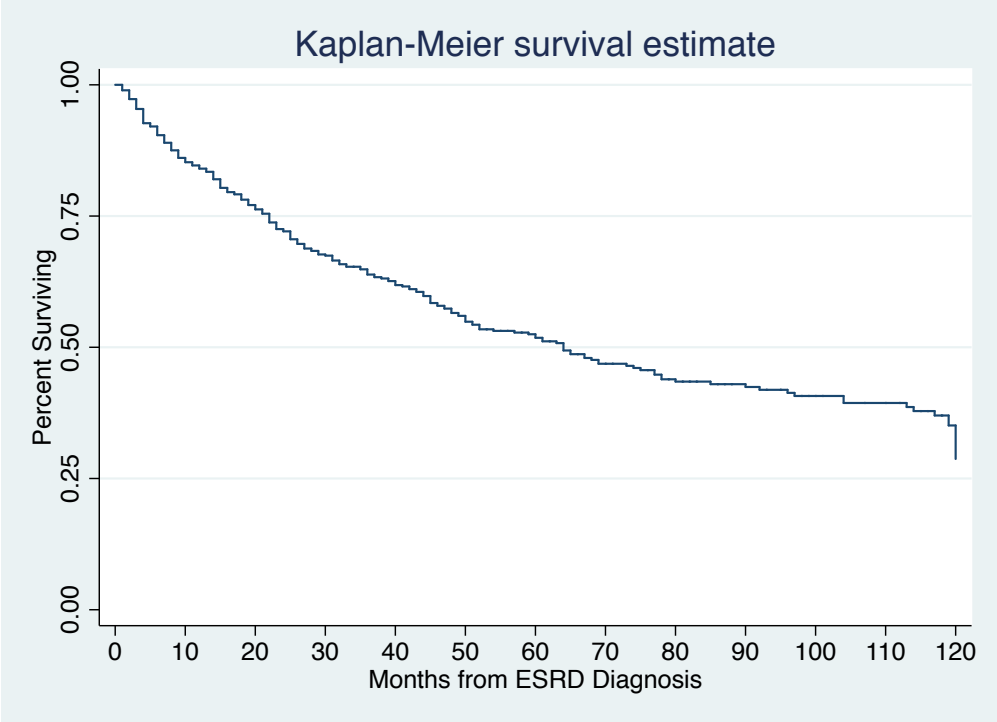
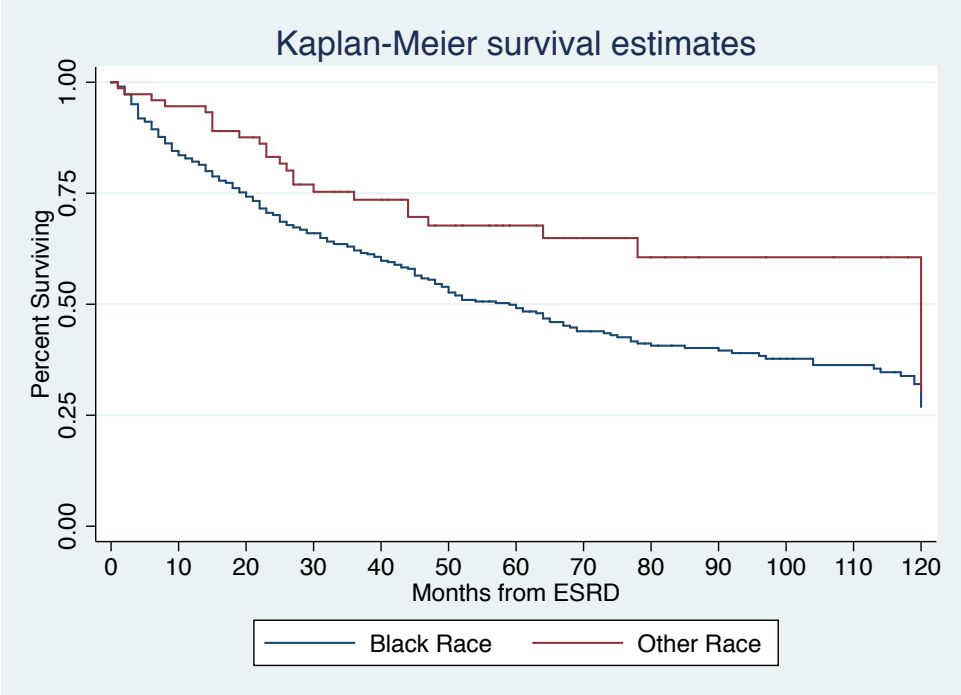
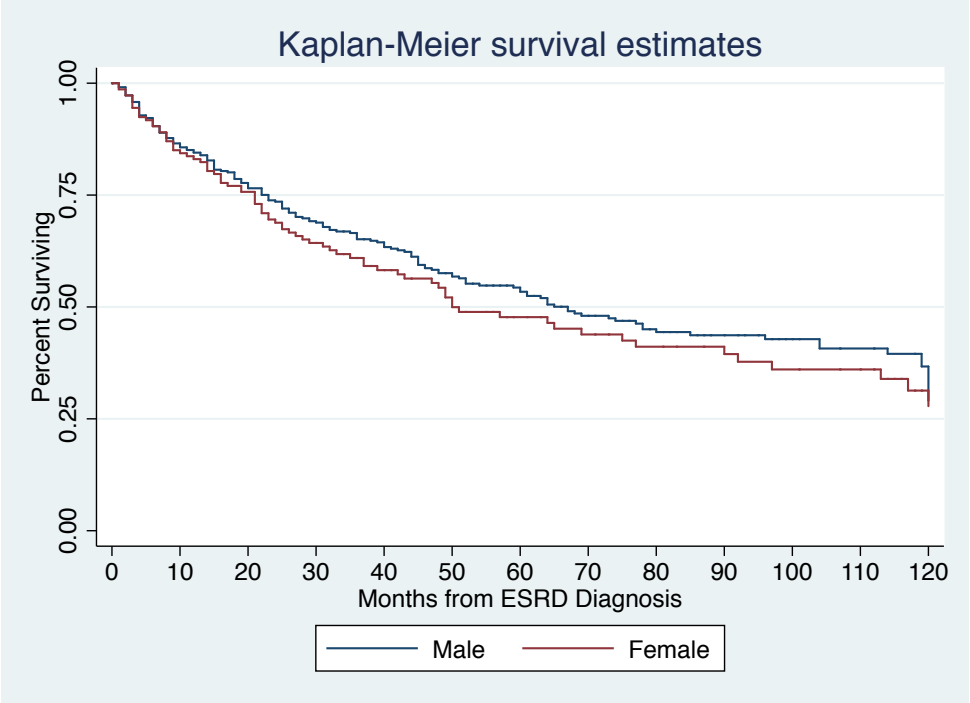


Figure 4. Kaplan-Meier Survival Estimate of HIV+ ESRD patients in NA-ACCORD, by Race



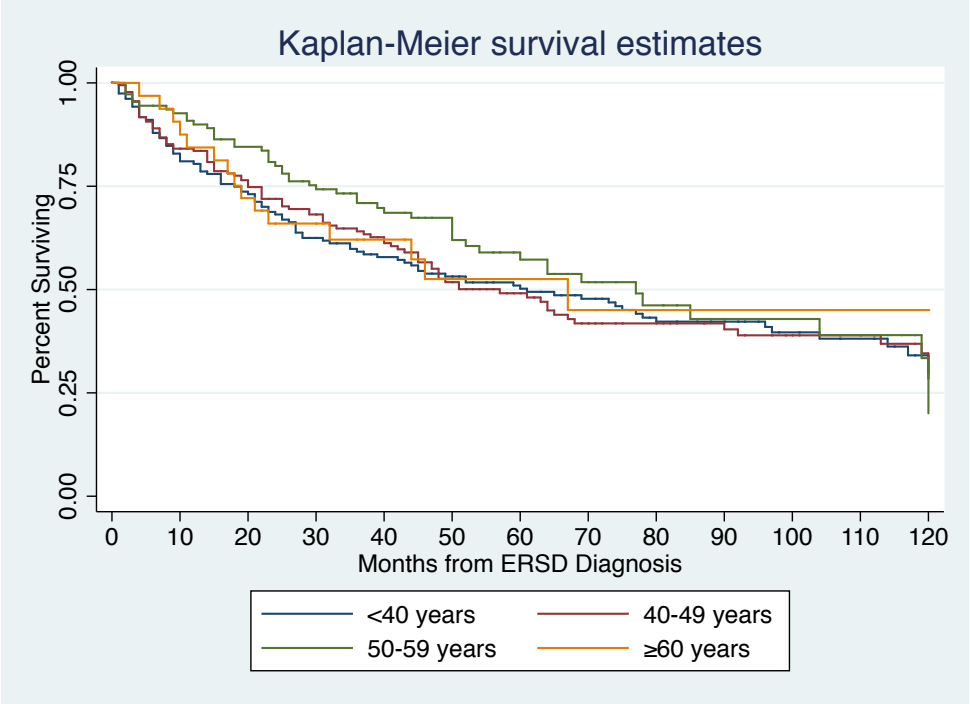
Log-rank p-value: 0.005

Figure 5. Kaplan-Meier Survival Estimate of HIV+ ESRD patients in NA-ACCORD, by Sex



Log-rank p-value: 0.33

Figure 6. Kaplan-Meier Survival Estimate of HIV+ ESRD patients in NA-ACCORD, by Baseline Age



Log-rank p-value: 0.63

Table 5. Standardized Mortality Ratio by Age, Years 2005-2010

Age group	Age-specific MR from USRDS (per 1 person-year)	Number of person-years in NA-ACCORD	Expected number of deaths	Observed number of deaths
20-29	0.0315	24.8333	0.7823	2
30-39	0.0443	224.5000	9.9491	29
40-49	0.0685	453.9167	31.1009	36
50-59	0.1080	355.7500	38.4329	31
60-64	0.1501	62.6667	9.4063	8
65-69	0.1946	42.5833	8.2860	4
70-74	0.2512	21.0000	5.2745	1
75-79	0.3239	2.8333	0.9176	2
80-84	0.4106	0.0000	0.0000	0
85+	0.5262	0.3333	0.1754	1
Total			104.3248	114
	Age-specific SMR:	**1.0927**	**95% CI:**	**(0.89, 1.29)**

MR = mortality rate
Mortality rates are from 2014 USRDS data, retrieved from http://www.usrds.org/reference.aspx, Table H.2
NA-ACCORD person-years are derived from person-months divided by 12

Table 6. Standardized Mortality Ratio by Sex, Years 2005-2010

Sex	Sex-specific MR from USRDS (per 1 person-year)	Number of person-years in NA-ACCORD	Expected number of deaths	Observed number of deaths
Male	0.1592	854.0833	135.9274	78
Female	0.1680	338.2500	56.8204	36
Total			192.7477	114
	Sex-specific SMR:	**0.5914**	**95% CI:**	**(0.48, 0.70)**

MR = mortality rate
Mortality rates are from 2014 USRDS data, retrieved from http://www.usrds.org/reference.aspx, Table H.2
NA-ACCORD person-years are derived from person-months divided by 12

Table 7. Standardized Mortality Ratios, by Race, Years 2005-2010

Race	Age-specific MR from USRDS (per 1 person-year)	Number of person-years in NA-ACCORD	Expected number of deaths	Observed number of deaths
White	0.1791	84.9167	15.2043	9
Black	0.1445	961.5000	138.9207	99
Other	0.1215	145.9167	17.7289	6
Total			171.8539	114
	Race-specific SMR:	**0.6634**	**95% CI:**	**(0.52, 0.79)**

MR = mortality rate
Mortality rates are from 2014 USRDS data, retrieved from http://www.usrds.org/reference.aspx, Table H.2
NA-ACCORD person-years are derived from person-months divided by 12

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PROFILE

Master of Health Science candidate concentrating in infectious disease epidemiology, with a research focus on HIV/AIDS. Certified HIV tester and counselor in the state of Maryland. Particular interest in social and behavioral aspects of health behaviors, including prevention, care-seeking, and treatment, particularly in marginalized populations. Strong quantitative and qualitative epidemiological skills.

EDUCATION

Master of Health Science in Epidemiology (MHS), GPA: 3.89/4.0
Expected May 2015
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Concentration: Infectious Disease Epidemiology
Relevant Coursework (to be completed by May 2015): 4 terms of Epidemiologic Methods; 4 terms of Biostatistics; 4 Terms of Infectious Disease Epidemiology; 2 Terms of HIV/AIDS Epidemiology; 1 Term of Genetic Epidemiology; Practical Skills in Conducting Research in Clinical Epidemiology; Epidemiologic Inference in Outbreak Investigations; Psychosocial Factors in Health and Illness; Introduction to the U.S. Healthcare System; Professional Epidemiology
Honors: Delta Omega, Master's Tuition Scholarship

Bachelor of Arts in Comparative Human Development, GPA: 3.89/4.0
June 2013
The University of Chicago, Chicago, IL
Honors: Phi Beta Kappa (Junior Year); Dean's List 2010, 2011, 2012, 2013

WORK EXPERIENCE

Research Assistant
August 2014 – Present
Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, Baltimore, MD

- Analyze patient data from The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) to characterize survival after End Stage Renal Disease (ESRD) diagnosis in HIV positive individuals
- Compare age-, sex-, and race-adjusted mortality rates after ESRD diagnosis in HIV positive adults with that of the general population utilizing SAS and Stata software packages

Teaching Assistant, *Principles of Epidemiology*
July 2014 – August 2014
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

- Led laboratory sessions two times per week, introducing new concepts and answering lab-specific questions
- Tutored students on concepts introduced in lectures during established office hours once per month
- Corrected students' midterm and final examinations as well as weekly laboratory exercises

HIV Tester and Counselor
October 2013 – May 2014
Johns Hopkins Children's Center Harriet Lane Clinic, Baltimore, MD

- Administered OraQuick (oral) or Clearview (blood) rapid HIV test; provided patients with HIV test results and appropriate information concerning next steps
- Educated and counseled patients about HIV/STD risk reduction behaviors and strategies; provided reproductive health options to patients; connect patients to relevant resources or sources of information

Research Assistant
October 2012 – June 2013
The University of Chicago Medical Center, Section of Infectious Diseases, Chicago, IL

- Collected and analyzed data for Dr. Michael David for the purpose of identifying risk factors for recurrent community-associated MRSA infections
- Compiled quantitative and qualitative data from the University of Chicago Medical Center doctors and past patients for an NIH-funded prospective cohort study on recurrent infections

Research Assistant
June 2011 – October 2011
The Harris School of Public Policy Studies at the University of Chicago, Chicago, IL

- Collected and interpreted sociological data analyzing the impact of economic disparities on education throughout the world through a collaboration with Professors Susan Mayer and Leonard Lopoo (Syracuse University)
- Compared social and economic variables among the 50 states and among OECD countries using Microsoft Excel

Teaching Assistant, ***Eliminating Infectious Disease*** September 2010 – December 2010
University of Chicago, The Division of Biological Sciences**,** Chicago, IL

- Tutored students during personal office hours four times per week for between two to three hours per day; coordinated review sessions; held office hours; corrected students' term papers and examinations

LEADERSHIP ACTIVITIES

Project Manager
October 2013 – Present
Thread, Baltimore, MD

- Lead group of volunteers as head mentor for an underperforming Baltimore high school student
- Oversee and collaborate with team of mentors to help student achieve academic and social goals
- Work with Program Coordinator to develop and execute project plans and timelines
- Connect with external contacts as needed to provide personal support for student mentee

Social Chair
September 2014 – Present
Epidemiology Student Organization, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

- Establish quarterly inter- and intra-department events including annual department-wide picnic
- Collaborate with Epidemiology Student Organization leadership to plan student and faculty gatherings

PROFESSIONAL DEVELOPMENT

Computer Skills: Stata; SAS; PC and Mac Microsoft Word, Excel, and PowerPoint
Certifications: Maryland Department of Health and Mental Hygiene, Prevention and Health Promotion Administration's HIV 101 Training for Testing and Counseling
Language: Proficient in French